Variation of Serum Prostate-Specific Antigen Levels

An Evaluation of Year-to-Year Fluctuations

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Context Serum prostate-specific antigen (PSA) testing is frequently used in early detection programs for prostate cancer. While PSA testing has resulted in an increase in prostate cancer detection, its routine use has been questioned because of a lack of specificity.

Objective To determine whether year-to-year fluctuations in PSA levels are due to natural variation and render a single PSA test result unreliable.

Design, Setting, and Participants Retrospective analysis of an unscreened population of 972 men (median age, 62 years) participating in the Polyp Prevention Trial (1991-1998). Five consecutive blood samples were obtained during a 4-year period and were assessed for total and free PSA levels.

Main Outcome Measure Abnormal PSA test result based on a PSA level higher than 4 ng/mL; a PSA level higher than 2.5 ng/mL; a PSA level above the age-specific cutoff; a PSA level in the range of 4 to 10 ng/mL and a free-to-total ratio of less than 0.25 ng/mL; or a PSA velocity higher than 0.75 ng/mL per year.

Results Prostate biopsy would have been recommended in 207 participants (21%) with a PSA level higher than 4 ng/mL; in 358 (37%) with a level higher than 2.5 ng/mL; in 172 (18%) with a level above the age-specific cutoff; in 190 (20%) with a level between 4 and 10 ng/mL and a free-to-total ratio of less than 0.25 ng/mL; and in 145 (15%) with a velocity higher than 0.75 ng/mL per year. Among men with an abnormal PSA finding, a high proportion had a normal PSA finding at 1 or more subsequent visits during 4-year follow-up: 68 (44%) of 154 participants with a PSA level higher than 4 ng/mL; 116 (40%) of 291 had a level higher than 2.5 ng/mL; 64 (55%) of 117 had an elevated level above the age-specific cutoff; and 76 (53%) of 143 had a level between 4 and 10 ng/mL and a free-to-total ratio of less than 0.25 ng/mL.

Conclusion An isolated elevation in PSA level should be confirmed several weeks later before proceeding with further testing, including prostate biopsy.

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MEASUREMENTS OF SERUM prostate-specific antigen (PSA) levels in combination with digital rectal examination have long been recommended as part of an early detection program for prostate cancer.[1,2] Epidemiological data demonstrate a marked increase in the number of men diagnosed as having prostate cancer and a shift toward earlier-stage disease.[3-5] While many of these men are diagnosed as having localized and therefore potentially curable tumors, there has also been a substantial increase in the number of men undergoing radical prostatectomy for small cancers that may be clinically insignificant. Epstein et al[6] reviewed 157 men undergoing radical prostatectomy for clinical stage Tlc prostate cancer. Using a definition of insignificant cancer as a pathologically confined tumor with no Gleason component of 4 or 5, and a total tumor volume of less than 0.5 cm^3, these investigators found that 26% of their study population had insignificant disease. Similarly, Ohori et al[7] reported that 17% of men undergoing radical prostatectomy met the above definition for an insignificant tumor. These data suggest that while widespread use of PSA testing has resulted in the detection of earlier-

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stage cancers, many of these tumors were unlikely to be a threat to the overall health of the individual.

While PSA testing has resulted in an increase in prostate cancer detection, its routine use as a screening tool has been questioned because of a lack of specificity when levels are moderately elevated (4 to 10 ng/mL). Twenty-five percent of men with PSA levels in this range do have biopsy-proven prostate cancer, but 75% have negative biopsy results.[2] A variety of methods have been suggested to improve the specificity of PSA testing, including age-specific PSA reference ranges,[8] which normalize levels to a particular decade of life in an attempt to account for normal prostatic enlargement with age; PSA velocity,[9] which correlates change in PSA over time with the likelihood that this change may be associated with benign prostatic growth; and percentage-free PSA,[10,11] which accounts for the observation that men with benign prostatic hyperplasia are more likely to have PSA in an unbound state in the serum compared with men diagnosed as having prostate cancer. However, regardless of which serum PSA derivative is used, natural variations in PSA level may confound our ability to use PSA testing as a successful screening tool.

Natural biological variations in PSA levels have been previously studied. Nixon et al[12] evaluated daily biological variations of PSA levels by obtaining 10 serum samples from 24 patients during a 2-week period to determine the difference required between 2 consecutive PSA measurements that would indicate a significant elevation. These investigators concluded that the degree of biological variation differs among patients, such that an increase between 2 consecutive PSA levels that is less than 20% to 46% may be due to biological and analytical variation alone. Furthermore, they estimated that 3 consecutive PSA measurements would be needed to achieve an estimate of the mean concentration within 10% of the actual mean for half the patients, whereas 15 measurements would be needed to ensure that 95% of the population had estimated mean concentrations of PSA at the same level of accuracy. Similarly, Ornstein et al[13] examined the biological variation of total, free, and percentage-free PSA in 92 men who are older than 50 years. All men underwent PSA testing on 3 occasions, each 2 weeks apart. The study showed a mean variation of approximately 15% in measurements of total, free, and percentage-free PSA. These studies suggest that natural biological variation occurs in PSA testing in the short term.

In this investigation, we have taken advantage of a population of male participants in a colon polyp prevention trial who had blood drawn annually during a 4-year period. These samples were later analyzed to study natural variation in PSA levels. These men can be considered representative of the healthy population of men at risk for prostate cancer, who would be candidates for population-based screening. Our analysis focuses on the effect of PSA screening strategies for this population.

METHODS

We used data and blood samples from the Polyp Prevention Trial, a multicenter randomized trial designed to evaluate the effect of a diet low in fat and high in fiber, fruits, and vegetables on the recurrence of colorectal adenomas.[14-16] Participants were men and women aged 35 years or older with 1 or more adenomas. Recruitment was from 1991 through 1994. Participants were followed up from their baseline recruitment date for 4 years. The study was completed in 1998. At baseline and at each subsequent year of follow-up, participants completed food records, questionnaires, and health and lifestyle forms, and provided 3 fasting blood samples. Data and blood samples for each participant were labeled with a new record number by the central data center to ensure anonymity of the results. The protocol was approved by the institutional review boards of Memorial Sloan-Kettering Cancer Center (New York, NY) and the National Cancer Institute (Bethesda, Md). For this PSA analysis of the serum samples taken from the main trial, informed consent was waived. This was approved as exempt by the office of human subjects research of the National Cancer Institute with the stipulation that all specimens and data be made completely anonymous. It was approved by the institutional review board of Memorial Sloan-Kettering Cancer Center in 1998 with the understanding that the specimens and data be made completely anonymous. This was followed exactly as all serum samples and data provided by the National Cancer Institute were made completely anonymous and any links to the original data were broken.

For each sample, serum was separated from the clot, aliquotted, and frozen at −70°C in a central repository within 4 hours of the blood draw. Serum PSA testing was performed from mid-1999 through the beginning of 2000. Therefore, samples were stored between 1 and 9 years prior to their analysis. The stability of total PSA levels over this time frame has been previously documented.[17] The long-term stability of free PSA levels is unknown, although these levels are apparently stable for at least 39 months when stored under the conditions used in our study.[18] Samples were not thawed from the time of the initial freezing until PSA determinations were made. Coded specimen inventory listings were organized by subject, so that all specimens from a particular subject could be identified and assayed at the same time, thus eliminating the possibility of between-assay variability. Serum PSA concentration was measured by a heterogeneous sandwich magnetic separation assay using the Immuno 1 PSA assay (Bayer Diagnostics, Leverkusen, Germany). The PSA assay has a detection limit of 0.05 ng/mL. The coefficients of variation for the assay at concentrations of 0.7 ng/mL were 3.1%; 2.8 ng/mL, 2.9%; and 17.9 ng/mL, 0.6%. Samples with PSA levels between 4 and 10 ng/mL were also analyzed for free PSA by a 2-site immunoradiometric assay using monoclonal antibodies di-

rected against distinct antigen sites on the free-PSA molecule (Hybritech Tandem R, Hybritech, San Diego, Calif).

The Polyp Prevention Trial randomized 2079 men and women. The study design and results are described elsewhere.[14-16] There were 1351 male participants. We excluded participants with a prior history of prostate cancer (n=36). Cancer diagnoses were obtained from the health and lifestyle forms and from hospital records. Initially, we also excluded men with fewer than 2 serum samples (n=85), leaving 1230 male participants. However, since most of these participants (n=972; 79%) had PSA measurements at each of the 5 time points, we further restricted our cohort to these 972 participants. Results were not substantially different if all 1230 participants were included (data not shown). Stored blood from these participants was analyzed for PSA levels under the supervision of a single clinical chemist (M.F.), and for free PSA in samples for which the total PSA was between 4 and 10 ng/mL. Further details are available in an earlier report of the effect of dietary intervention on changes in PSA.[19]

Because there is no consensus as to what a healthy PSA level should be, we used a variety of PSA cutoffs to estimate the frequency of an abnormal result in our study population. These cutoffs included (1) any PSA level higher than 4 ng/mL,[1] (2) any PSA level higher than 2.5 ng/mL,[20] (3) age-specific PSA levels[8] (age <50 years: >2.5 ng/mL; age 50-59 years: >3.5 ng/mL; age 60-69 years: >4.5 ng/mL; age >70 years: >6.5 ng/mL), (4) free-to-total PSA ratio lower than 0.25 ng/mL among men with PSA levels between 4 and 10 ng/mL (as suggested in the *Guidelines for Interpretation of Results* for the Hybritech Tandem R assay),[11] and (5) PSA velocity higher than 0.75 ng/mL per year.[9]

RESULTS

A total of 972 men between the ages of 35 and 89 years (median age, 62 years) were included in this study. Baseline PSA levels by age group are presented in TABLE 1. A variety of PSA cutoffs were used to determine the number of men who met the criteria for prostate biopsy during the 4-year study period (TABLE 2). Using any of these PSA thresholds, 361 (37%) of the participants would have met at least 1 of the criteria for an abnormal PSA test result. This result is driven by the 2.5-ng/mL cutoff, which is the least restrictive criterion for prompting a biopsy. The other 4 criteria for prompting a biopsy would identify between 15% and 21% of the participants. If the 2.5-ng/mL criterion were excluded, 245 (25%) men would have been recommended for biopsy by exceeding 1 of the 4 remaining criteria. Of the men whose baseline PSA level was in the normal range, 12% experienced a subsequent PSA level higher than 4 ng/mL; 17% had a PSA level higher than 2.5 ng/mL; 9% and 10%, respectively, had age-specific and free-PSA ratio criteria.

We next sought to determine how often a participant's PSA level would return to normal the year after the level had been elevated. We considered 4 of 5 criteria in this analysis: PSA level higher than 4 ng/mL; PSA level higher than 2.5 ng/mL; age-specific PSA levels; and free-PSA ratio. Men who were documented as developing prostate cancer during the study period (n=37) were excluded. Although we cannot be sure that all diagnosed cases were reported, the expected number of incident cases in a population of this size and age distribution during the 4-year follow-up was 26. It is likely that few diagnosed cases were included erroneously. In any event, we further excluded 3 participants whose PSA profiles strongly indicated a diagnosis and treatment of prostate cancer. These individuals had an initial PSA level that was high and all subsequent levels were close to zero. For each remaining participant, we identified the first visit in which an abnormal PSA level was recorded. The PSA level at the subsequent visit (if available) was checked to see if it reverted to a result in the normal range (TABLE 3). There were 172 men in whom the PSA level was above the 4-ng/mL threshold at 1 or more visits. Of the 154 men for whom the first elevated PSA level did not occur at the final visit, 30% had a PSA level below 4 ng/mL at the next visit. The corresponding percentages of participants whose PSA levels returned to the normal range at the next visit were 26% for the PSA level higher than 2.5-ng/mL criterion; 37% for the age-specific criterion; and 35% for the free-PSA criterion. When we considered the number of men whose PSA level returned to the normal range at any subsequent visit, these percentages increase to 44% with a PSA level higher than 4 ng/mL; 40% with a PSA level higher than 2.5 ng/mL; 55% for the age-specific level; and 53% for the free-PSA level. The average number of patient visits (number of PSA levels) following the abnormal PSA level were 2.9, 3.0, 2.7, and 2.9, respectively, depending on the criterion (TABLE 4).

Table 1. Baseline PSA Levels by Age Group

Age, y	No. (%) of Participants	PSA Level at Baseline, ng/mL	
		Mean (95% CI)	Median (Range)
<50	102 (10)	0.8 (0.7-1.0)	0.7 (0.1-4.5)
50-59	289 (30)	1.5 (1.3-1.7)	1.0 (0.04-15.7)
60-69	371 (38)	2.3 (2.0-2.5)	1.5 (0.04-22.9)
70-79	201 (21)	2.8 (2.4-3.2)	2.0 (0.01-14.8)
≥80	9 (1)	4.4 (0-10.2)	1.4 (0.3-24.0)

Abbreviations: CI, confidence interval; PSA, prostate-specific antigen.

Table 2. Participants With PSA Levels Meeting Standard Criteria for Prostate Biopsy

Criterion	No. (%) of Participants
PSA level, ng/mL	
>4.0	207 (21)
>2.5	358 (37)
Age-specific PSA level	172 (18)
Free PSA ratio	190 (20)
PSA velocity	145 (15)
Any	361 (37)

Abbreviation: PSA, prostate-specific antigen.

For those men whose PSA levels returned to the normal range, we also determined if the decline in PSA level remained within the normal range on the subsequent PSA evaluation (TABLE 5). For the criteria used in our study, between 65% and 83% of participants maintained a normal PSA level on the next annual evaluation. To illustrate spontaneous variations in PSA levels over time, the FIGURE shows a random sample of participants with PSA levels greater than 4 ng/mL. Ten participants had an elevated PSA level that did not return to normal range (Figure, A) and 10 participants had an elevated PSA level that subsequently returned to normal (Figure, B).

COMMENT

The use of PSA testing as a screening tool for prostate cancer became widespread after its introduction more than a decade ago. This led to a rapid increase in prostate cancer incidence, but the impact on prostate cancer mortality is unclear. Two recent ecological studies show divergent results. In one study in a region of Austria in which PSA testing was made freely available to men aged 45 to 75 years, the region experienced a significant reduction in mortality compared with other regions of Austria.[21] However, in a similar comparison in the United States, 2 regions with different, although low, rates of PSA testing exhibited equivalent prostate cancer mortality.[22] More definitive randomized trials on this issue are in progress. At present, PSA testing is not recommended as a screening tool by the US Preventive Services Task Force[23] or by the Canadian Task Force on Preventive Health Care.[24] The National Cancer Institute defines PSA testing as a strategy that is still under investigation.[25]

Despite this, a PSA test is often used as part of an early detection program for prostate cancer, in part in response to public demand.[26] In a population-based study in New York State conducted during 1994 and 1995, 37% of white men aged 50 years or older and 26% of black men reported knowledge of having received a PSA test.[27] In addition, results from large-scale prostate cancer screening, such as Prostate Cancer Awareness Week[28] and a prospective trial of prostate cancer screening from 6 university centers,[1] demonstrated that approximately 10% to 15% of men in their initial year of screening will have a PSA level greater than 4 ng/mL and will be recommended to undergo a prostate biopsy. These results are similar to what was found in our study, in which 21% of men had a PSA level greater than 4 ng/mL over a 4-year period. Importantly, our results show that nearly half of men who had 1 abnormal PSA level subsequently had a normal level, suggesting that PSA level fluctuations may result in many false-positive elevations. While PSA testing does lead to the early detection of prostate cancer, a single abnormal PSA level should be viewed with caution. A newly elevated level should be confirmed before expensive or invasive tests, such as a prostate biopsy, are recommended.

Currently, there is no standardized policy for the examination of an elevated PSA level. Actual practice includes 3 likely scenarios. The first is immediate referral for prostate biopsy. This discounts any potential role for random fluctuations in PSA levels, or the possibility of laboratory error. The second is immediate repeat of the PSA test. This decision assumes a potential laboratory error. If the repeat test result is another elevated PSA level, a biopsy is usually recommended. However, if the

Table 3. Initial Abnormal PSA Level Returned to Normal on Next PSA Test

Criterion	No. of Participants		No. (%) of Participants With Normal Next Time After Abnormal PSA Level
	Abnormal PSA Level*	Returned for Next Visit	
PSA level, ng/mL			
>4.0	172	154	46 (30)
>2.5	319	291	76 (26)
Age-specific PSA level	139	117	43 (37)
Free PSA ratio	156	143	50 (35)

Abbreviation: PSA, prostate-specific antigen.
*Excludes 37 men diagnosed as having prostate cancer and 3 men with a marked drop in PSA level, which suggested they were receiving treatment.

Table 4. Initial Abnormal PSA Level Returned to Normal at Any Subsequent Visit

Criterion	No. of Participants		No. (%) of Participants With Normal Level at Any Subsequent Visit
	Abnormal PSA Level*	Returned for Subsequent Visit	
PSA level, ng/mL			
>4.0	172	154	68 (44)
>2.5	319	291	116 (40)
Age-specific PSA level	139	117	64 (55)
Free PSA ratio	156	143	76 (53)

Abbreviation: PSA, prostate-specific antigen.
*Excludes 37 men diagnosed as having prostate cancer and 3 men with a marked drop in PSA, which suggested they were receiving treatment.

Table 5. Participants With Abnormal and Subsequent Normal PSA Levels

Criterion	No. of Participants With Previous Abnormal Level	No. (%) of Participants With Levels Remaining Normal on 2 Consecutive Tests
PSA level, ng/mL		
>4.0	40	32 (80)
>2.5	62	40 (65)
Age-specific PSA level	35	29 (83)
Free PSA ratio	43	32 (74)

Abbreviation: PSA, prostate-specific antigen.

repeat PSA test result is a normal level, the participant is not referred for further testing, but has continued PSA testing on an annual or semiannual basis. The third is to wait 4 to 6 weeks, usually requesting that the participant take antibiotics with or without an antiinflammatory agent, and then have a repeat PSA test. This assumes an infection and/or inflammation as the cause of the elevated PSA level, which will resolve with time and/or treatment. We found a substantial percentage of elevated PSA levels that spontaneously returned to normal. In our study, PSA levels were assessed annually, so we have no data on the amount of time required for a newly elevated PSA level to return to baseline. Other studies report 4 to 6 weeks for the PSA level to return to baseline after a prostate biopsy or transurethral resection of prostate.[29] It seems reasonable to wait at least this long before repeating a PSA test.

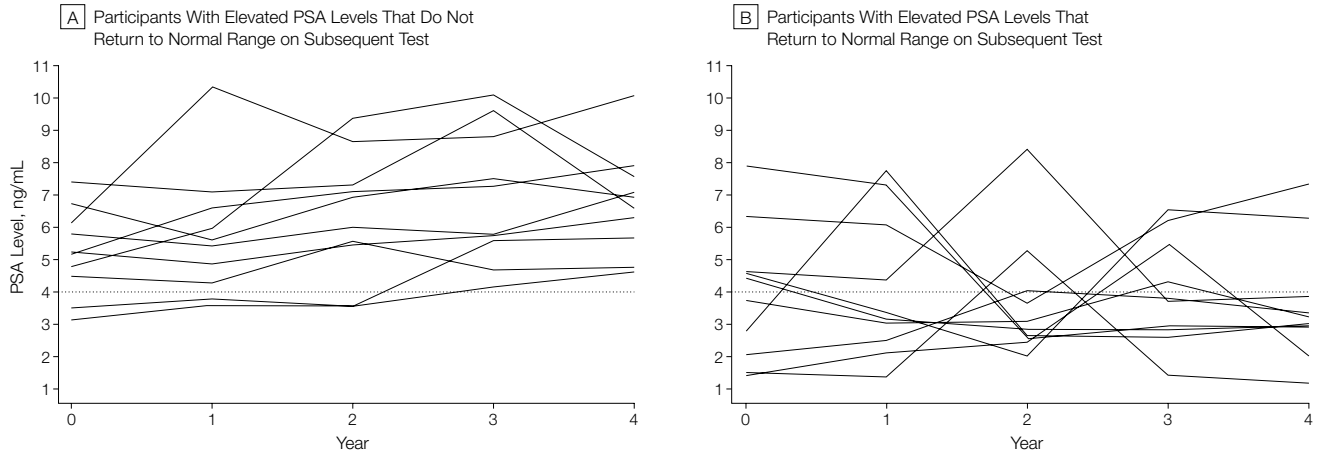
A policy of confirming an abnormal PSA result certainly has important public health considerations. If a significant proportion of participants have a normal PSA level on subsequent testing, the cost-savings would be substantial because these men would not be referred for prostate biopsy. Prostate biopsy is generally safe, but infections have been reported in 1% to 7%,[30] and hematuria in 2% to 4%.[31] A policy of confirming newly elevated PSA levels several weeks later may reduce the number of unnecessary procedures markedly. The most important benefit, however, could be a reduction in the diagnosis of cancer in men with small incidental tumors, who would be subjected to the morbidity of definitive treatment for what could be a pseudodisease that presents no threat to their life or health.

Of course, a policy of confirmation after 4 to 6 weeks could, theoretically, allow growth and spread of a malignant tumor. This concern seems unfounded in regard to prostate cancer. Cancer progression in "watchful waiting" trials support the concept that prostate cancer has a prolonged natural history. Epstein et al[32] studied 70 men with clinical stage T1c prostate cancer who underwent watchful waiting with repeat needle sampling to assess progression. Of 70 cases, 9 (12.9%) showed an increase in Gleason grade from 6 or less to 7 or greater. They concluded that a delay of several months between biopsy and surgical therapy was no cause for concern. Lastly, Stamey and Kabalin[33] examined serial PSA levels in men with untreated prostate cancer. These investigators concluded that the rate of increase of PSA levels in men with clinical stage T1 or T2 prostate cancer suggested a doubling time of at least 2 years. Furthermore, data in the recent Swedish randomized trial of radical prostatectomy vs watchful waiting showed no difference in time to metastases for the first 5 years after treatment, suggesting that delay in diagnosis of a few weeks or months is unlikely to alter treatment efficacy.[34] One can extrapolate these results to suggest that men should not be concerned about waiting several weeks to confirm an elevated PSA level before proceeding to prostate biopsy.

A potential limitation of our study is that we cannot be certain that men have not been diagnosed as having prostate cancer without our knowledge during the study period. This seems unlikely, however. Each participant completed an annual health summary that requested information regarding new medical problems, including a new diagnosis of malignancy. Men diagnosed as having prostate cancer usually undergo treatment. Men treated with radical prostatectomy or hormonal therapy would have had a marked decline in PSA level that would have been noted during annual testing.

Another limitation is the lack of biopsy data in men who developed an elevated PSA level during this trial. Some of these men may have had prostate cancer. Nevertheless, there is little risk in waiting to confirm a sustained in-

Figure. Random Sample of Participants



Participants had prostate-specific antigen (PSA) levels of greater than 4 ng/mL.

crease in PSA level before proceeding with a diagnostic biopsy. Because of the apparent fluctuations in PSA levels over time, this policy would decrease the number of unnecessary biopsies, but still diagnose men within a reasonably safe time frame.

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